General

Guideline Title

Adult depression in primary care.

Bibliographic Source(s)

Mitchell J, Trangle M, Degnan B, Gabert T, Haight B, Kessler D, Mack N, Mallen E, Novak H, Rossmiller D, Setterlund L, Somers K, Valentino N, Vincent S. Adult depression in primary care. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Sep. 129 p. [334 references]

Guideline Status

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 10, 2016 – Olanzapine : The U.S. Food and Drug Administration (FDA) is warning that the antipsychotic medicine olanzapine can cause a rare but serious skin reaction that can progress to affect other parts of the body. FDA is adding a new warning to the drug labels for all olanzapine-containing products that describes this severe condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- May 3, 2016 – Aripiprazole (Abilify, Abilify Maintena, Aristada) : The U.S. Food and Drug Administration (FDA) is warning that compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex have been reported with the use of the antipsychotic drug aripiprazole (Abilify, Abilify Maintena, Aristada, and generics). These uncontrollable urges were reported to have stopped when the medicine was discontinued or the dose was reduced. These impulse-control problems are rare, but they may result in harm to the patient and others if not recognized.

Recommendations

Major Recommendations

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): For a description of what has changed since the previous version of this guidance, refer to Summary of Changes Report -- September 2013 . In addition, ICSI has made a decision to transition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as a method of assessing the quality of evidence and writing recommendation.

The recommendations for the diagnosis and treatment of major depression in adults in primary care are presented in the form of a table with a list of evidence-based recommendations and an algorithm with 12 components, accompanied by detailed annotations. An algorithm is provided in the original guideline document at the ICSI Web site for Adult Depression in Primary Care. Clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Quality of evidence (Low Quality, Moderate Quality, and High Quality) and strength of recommendation (Weak or Strong) ratings are defined at the end of the "Major Recommendations" field.

Clinical Highlights

- A reasonable way to evaluate whether a system is successfully functioning in its diagnosis, treatment plan, and follow-up of major depression is to consider:
    - How well the diagnosis is documented
    - How well the treatment team engages and educates patients/families
    - How reliably the ongoing patient contacts occur and response/remission to treatment are documented
    - How well the outcomes are measured and documented

  (*Introduction; Annotations #1, 2, 8, 9, 10; Aims #1, 6, 7*)

- Use a standardized instrument to document depressive symptoms. Document baseline symptoms and severity to assist in evaluating future progress, including response and remission rates. (*Annotation #1, 2; Aims #1, 3*)
- Additional considerations that should be taken into account:
    - Patients with a high risk of common comorbid depression conditions such as substance misuse, diabetes, cardiovascular disease and chronic pain should be screened for depression.
    - Perinatal depression treatment involves a thorough risk-benefit assessment in order to minimize the risks of both depression and its treatment to the mother and child.
    - Older persons and the cultural experiences of patients should receive special considerations regarding risk, assessment and treatment of depression.

  (*Annotation #6; Aims #3*)

- Antidepressant medications and/or referral for psychotherapy are recommended as treatment for major depression. Factors to consider in making treatment recommendations are symptom severity, presence of psychosocial stressors, presence of comorbid conditions, and patient preferences. Physical activity and active patient engagement are also useful in easing symptoms of major depression. (*Annotation #8; Aim #6*)
- If the primary care clinician is seeing incremental improvement, continue working with the patient to increase medication dosage or augment with psychotherapy or medication to reach remission. This can take up to three months. Studies have shown that depression can be treated successfully in primary care. (*Annotation #8, 9, 10*)
    - For medication treatment, patients may show improvement at two weeks but need a longer length of time to really see response and remission. Most people treated for initial depression need to be on medication at least 6 to 12 months after adequate response to symptoms. Patients with recurrent depression need to be treated for three years or more. (*Annotation #11*)
    - For psychotherapy treatment, 8 to 10 weeks of regular and frequent therapy may be required to show improvement. (*Annotation #11*)
- The key objectives of treatment are to:
    - Achieve remission of symptoms in the acute treatment phase for major depression
    - Reduce relapse and reduction of symptoms
    - Return patient to previous level of occupational and psychosocial function

  (*Annotation # 10, 11; Aims #6*)

Adult Depression in Primary Care Algorithm Annotations

1. Depression Suspected
   Recommendation:

   - Clinicians should use a standardized instrument to screen for depression if it is suspected based on risk factors or presentation *(Low Quality Evidence, Strong Recommendation)*.

   Common Presentations

   Common presentations for patients not complaining of major depression or anhedonia include:

   - Multiple (more than five per year) medical visits
   - Multiple unexplained symptoms
   - Work or relationship dysfunction
   - Dampened affect
   - Changes in interpersonal relationships
   - Poor behavioral follow-through with activities of daily living or prior treatment recommendations
   - Weight gain or loss
   - Sleep disturbance
   - Fatigue
   - Memory/other cognitive complaints such as difficulty concentrating or making decisions
   - Irritable bowel syndrome
   - Volunteered complaints of stress or mood disturbance

   Since medical illness does co-exist in patients with primary mood or anxiety disorders, it is necessary that physical complaints not be dismissed and/or merely accounted for as part of the depression. Medical issues should still be specifically addressed, especially when new symptoms are reported.

   The close relationship of mind and body results in the presentation of medical illness with major depression in various forms:

   - Medical illness may be a biological cause (e.g., thyroid disorder, stroke).
   - Medical illness or patient's perception of his or her clinical condition and health-related quality of life may trigger a psychological reaction to prognosis, pain or disability (e.g., in a patient with cancer).
   - Medical illness may exist coincidentally in a patient with primary mood or anxiety disorder.

   Non-Mood Presentations

   Non-mood presentations of major depression include fatigue, pain or other somatic complaints, sleep disturbances, sexual dysfunction, multiple medical visits and work or relationship dysfunction.

   A mood disorder (major depression, persistent depressive disorder or bipolar) may be present in 39% of patients with a presenting complaint of chronic fatigue (fatigue present at least half the time for at least one month) *[Low Quality Evidence]*.

   Major depression may also be associated with medical disorders or the patient's perception of his or her clinical condition. Although thyroid function abnormalities may cause depressive symptoms, screening for thyroid disease in all patients with major depression is not necessary because the prevalence of unidentified thyroid disease in patients with major depression is the same as in the general population *[Low Quality Evidence]*.

   Irritable bowel syndrome (IBS) is strongly correlated with psychiatric illness. Treatment of the underlying psychiatric disease may provide more than adequate management of IBS *[Low Quality Evidence]*.

   For women, severe obesity (body mass index greater than 40) has been strongly associated with depression *[Low Quality Evidence]*.

   Major depression is also seen in elderly patients with comorbid illnesses, such as cerebral vascular accident (CVA), cancer, dementia or disabilities.

   See also Annotation #6, "Additional Considerations (Medical Comorbidity, Cultural Considerations, Special Populations)?" in the "Medical Comorbidity" section.

   Risk Factors

   Risk factors for major depression include:

   - Family or personal history of major depression and/or substance abuse

- Recent loss
- Chronic medical illness
- Stressful life events that include loss (death of a loved one, divorce)
- Traumatic events (car accident)
- Major life changes (job change, financial difficulties)
- Domestic abuse or violence

Patients with chronic illnesses such as diabetes, cardiovascular disease and chronic pain are at higher risk for depression.

One previous episode of major depression is associated with a 50% chance of a subsequent episode, two episodes with a 70% chance, and three or more episodes with a 90% chance *[Low Quality Evidence]*.

Most studies indicate that in 40% to 60% of patients, a major life event precedes the first episode of major depression *[Low Quality Evidence]*.

If You Suspect Depression, Screen for It

Validated and reliable tools can help clinicians identify and systematically monitor patients with major depression. Use screening and tracking tools to enhance but not replace the clinical interview.

Either the Patient Health Questionnaire (PHQ)-2 or the PHQ-9 can be used to screen for depression. There is stronger evidence supporting the use of the PHQ-9 in patients with chronic disease.

Use the PHQ two-question tool in routine screening settings *[Meta-analysis]*.

Over the past two weeks, have you been bothered by:

- Little interest or pleasure in doing things?
- Feeling down, depressed or hopeless?

If the patient answers "yes" to either of the above questions, administer the full PHQ-9 depression instrument *[Systematic Review]*.

The PHQ-9 has been validated for measuring depression severity *[Low Quality Evidence]* and is validated as a tool for both detecting and monitoring depression in primary care settings *[Systematic Review]*.

It can be administered telephonically *[Low Quality Evidence]* and read to the patient. Elderly patients with mild cognitive impairment can reliably fill out the PHQ-9 *[Low Quality Evidence]*. A recent study found the PHQ-9 useful in psychiatric practices, as well. PHQ-9 scores influenced clinical decision-making for 93% of more than 6,000 patient contacts *[Low Quality Evidence]*.

Other recognized and validated tools include the Beck Depression Inventory, Hamilton Rating Scale for Depression (HAM-D), and the Quick Inventory of Depressive Symptomatology Self Report (QID-SR) *[Low Quality Evidence]*. See the Appendices in the original guideline document for example questionnaires.

Regardless of the screening tool chosen, it is crucial to document that the patient meets the criteria of at least five symptoms for at least two weeks as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for major depression. One of the symptoms must be depressed mood or loss of interest or pleasure.

The primary objective is to use a standardized instrument that will quantify baseline intensity and document future progress, including response and remission rates.

Use of tools with diverse populations. The factor structure of the nine items in the PHQ-9 is comparable when tested with African Americans, Chinese Americans, Latino and non-Hispanic white patient groups *[Low Quality Evidence]*. Other language versions that are validated for use in primary care are Spanish *[Low Quality Evidence]* and Chinese *[Low Quality Evidence]*.

The tool and many other language versions can be found at http://www.phqscreeners.com. When administering the PHQ-9, be aware of cultural factors and involve an interpreter if needed. As research develops on risk adjustment and stratification using this tool, the work group will report and refine recommendations.

See also Annotation #6, "Additional Considerations (Medical Comorbidity, Cultural Considerations, Special Populations)?", below for more information on cultural beliefs and common presentations.

Clinicians should choose the screening method that best fits their personal preference, the patient population served and the practice setting.

2. Diagnose and Characterize Major Depression with Clinical Interview
   Recommendation:

   - Clinicians should use the DSM-5 criteria to determine a diagnosis of major depression, persistent depressive disorder, other specified depressive disorder and unspecified depressive disorder *(Low Quality Evidence, Strong Recommendation)*.

   Criteria Required for Diagnosis

   Depressed mood or anhedonia (diminished interest or pleasure in activities) is necessary to diagnose major depression.

   The use of a mnemonic may be helpful for remembering the symptoms of major depression and depressive disorder. SIGECAPS or SIG + Energy + CAPS is easily remembered and can be used in the clinical interview. Developed by Dr. Carey Gross of Massachusetts General Hospital, it stands for:

   > Sleep disorder (increased or decreased)
   > Interest deficit (anhedonia)
   > Guilt (worthlessness, hopelessness, regret)
   > Energy deficit
   > Concentration deficit
   > Appetite disorder (increased or decreased)
   > Psychomotor retardation or agitation
   > Suicidality

   DMS-V Criteria: Major Depressive Episode

   To qualify for a diagnosis of major depressive episode, the patient must meet criteria A through E:

   A. Five or more of the following symptoms have been present and documented during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
      Note: Do not include symptoms that are clearly attributable to another medical condition.

      1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful)
      2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
      3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
      4. Insomnia or hypersomnia nearly every day
      5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
      6. Fatigue or loss of energy nearly every day
      7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
      8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
      9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

   B. The symptoms do not meet criteria for a mixed episode.
   C. The episode is not attributable to the physiological effects of a substance or to another medical condition.
      Note: Criteria A-C represent a major depressive episode.

      Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history of and the cultural norms for the expression of distress in the context of loss.

   D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform

disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.
   Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Severity is based on the number of criterion, the severity of those symptoms and the degree of functional disability.

Refer to the original guideline document for description of mild, moderate, and severe episodes and other classifications of major depressive episodes and the corresponding International Classification of Diseases (ICD)-10 codes.

DMS-5 Criteria: Persistent Depressive Disorder

This disorder represents a consolidation of the DSM-IV-defined chronic major depressive disorder and dysthymic disorder. To qualify for a diagnosis of persistent depressive disorder, the patient must meet criteria A through H:

A. Depressed mood for most of the day, for more days than not, as indicated by either subjective account of observation by others, for at least two years.
B. Presence while depressed of two or more of the following:
   1. Poor appetite or overeating
   2. Insomnia or hypersomnia
   3. Low energy or fatigue
   4. Low self-esteem
   5. Poor concentration or difficulty making decisions
   6. Feelings of hopelessness
C. During the two-year period of the disturbance, the individual has never been without the symptoms in criteria A and B for more than two months at a time.
D. Criteria for major depressive disorder may be continuously present for two years.
E. There has never been a manic episode or hypomanic episode, and criteria have never been met for cyclothymic disorder.
F. The disturbance is not better explained by persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum or other psychotic disorder.
G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).
H. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

Note: Because the criteria for a major depressive episode include four symptoms that are absent from the symptom list for persistent depressive disorder, a very limited number of individuals will have depressive symptoms that have persisted longer than two years but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder is warranted.

Severity is based on the number of criterion, the severity of those symptoms and the degree of functional disability.

- Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning.
- Moderate: The number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for "mild" and "severe."
- Severe: The number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning.

[Guideline]

Refer to the original guideline document for information on other specified depressive disorder, unspecified depressive disorder, and alternate diagnosis including anxiety or somatoform disorder, adjustment disorder, and bipolar disorder.

Obtain Patient History

History of Present Illness

Determine history of present illness:

- Onset may be gradual over months or years or may be abrupt.

- Severity of symptoms and degree of functional impairment (mild moderate, severe)
- Determine prior history: number and severity of previous episodes, treatment responses and suicide attempts
- Ask about concurrent psychiatric conditions. Obtaining a past psychiatric history is important in terms of understanding prognosis and risk factors. For example, knowing past episodes of major depression, past co-occurring mental/behavioral health conditions, and past self-harm attempts helps establish risk and need to involve other mental health professionals.
- Assess psychosocial stressors (significant loss, conflict, financial difficulties, life change, abuse). Consider duration and severity of stressor(s) and likelihood for spontaneous improvement.

For short-term subclinical and mild cases, close follow-up and monitoring are still needed *[Meta-analysis]*. Ongoing utility of behavioral activation, skill building and self-management practices is recommended *[Meta-analysis]*, *[High Quality Evidence]*.

For more information, see Annotation #8, "Comprehensive Treatment Plan with Shared Decision-Making," sections titled "Behavioral activation – scheduled pleasant activities" and "Discuss Treatment Options."

Medical History

It is important to consider medical conditions that may mimic or directly cause symptoms of depression. A past medical history and brief review of systems is generally sufficient to rule out medical disorders causing major depression.

Examples of such disorders include:

- Dementia
- Delirium
- Hypothyroidism
- Parkinson's disease
- Stroke
- Connective tissue diseases

A review of the patient's medication and substance use may also provide an explanation for depressive symptoms. Sedatives, withdrawal from stimulants and other specific medications (e.g., interferon alpha, varenicline) may be contributing.

Review of the patient's medical history may find conditions that can impact pharmacological treatments: for example, prostatism, cardiac conduction abnormalities and impaired hepatic function.

Perform a focused physical examination and laboratory testing as indicated by the review of systems. The benefit of screening laboratory tests, including thyroid tests, to evaluate major depression has not been established.

Considerations of laboratory tests should be greater if:

- The medical review of systems detects symptoms that are rarely encountered in mood or anxiety disorders
- The patient is older
- The first major depressive episode occurs after the age of 40
- The depression does not respond fully to routine treatment

Medication History and Substance Abuse/Dependence

Determine medication history and substance abuse/dependence:

- Medications such as steroids, interferon, alpha-methyldopa, isotretinoin, varenicline, and hormonal therapy may be associated with major depression.
- Use of alcohol and hypnotics might mimic and/or induce depression, and comorbidity is common *[High Quality Evidence]*.
- Withdrawal from cocaine, anxiolytics, and amphetamines may mimic depression.
- Idiosyncratic reactions to other medications can occur. If possible, a medication should be stopped or changed if depression develops after beginning its use. If symptoms persist after stopping or changing medication, reevaluate for a primary mood or anxiety disorder.

4. Use Organization's Protocol If Available to Assess and Minimize Suicide Risk/Involve Mental Health Specialists
   Assess Suicidal Tendencies

   Assessing suicidal tendencies is a critical but often difficult process with a depressed patient. Consider asking and documenting the following progression of questions.

1. Do you feel that life is worth living?
2. Do you wish you were dead?
3. Have you thought about ending your life?
4. If yes, have you gone so far as to think about how you would do so? Be specific, what method would you use?
5. Do you have access to a way to carry out your plan?
6. What keeps you from harming yourself?

Many patients will not answer #4 directly or will add, "But I'd never do it." Give them positive feedback (e.g., "I'm glad to hear that") but do not drop the subject until she/he has told you the specific methods considered (e.g., gun, medication overdose, motor vehicle accident).

Develop a Suicide Protocol

It is important for a health care clinic to develop its own suicide protocol, taking into account the organization's workflow and resources. Each individual clinic should determine:

- A clear process for risk assessment
- When to involve the on-call mental health clinician
- Use of local or national hotlines
- Next steps

A recommended resource for establishing a clinic-based protocol to assess and minimize suicide risk is Bonner, L., et al. Suicide Risk Response: Enhancing Patient Safety Through Development of Effective Institutional Policies. Advances in Patient Safety: From Research to Implementation. Vol 3, February 2005 http://www.ahrq.gov/qual/advances/ .

See also Appendix C, "Example Suicidality Screening Flow," in the original guideline document.

Involve Mental Health Specialists

Involve same-day mental-health for any of these situations:

- Suicidal thoughts and/or plans that make the clinician uncertain of the patient's safety
- Assaultive or homicidal thoughts and/or plans that make the clinician uncertain about the safety of the patient or others
- Recent loss of touch with reality (psychosis)
- Inability to care for self/family

Involvement could include:

- Appointment with psychiatrist and/or psychotherapist
- Phone consultation with psychiatrist and/or psychotherapist
- Referral to the emergency department

[Low Quality Evidence]

Refer to the original guideline document for more information regarding risk factors for suicide and interventions to prevent suicide.

5. Assess for the Presence of Substance Misuse or Psychiatric Comorbidity If Suspected
Substance Abuse Prevalence

Alcoholism and major depressive disorder are distinct clinical entities. They are not different expressions of the same underlying condition. Within the general population, substance abuse prevalence ranges from 8% to 21% in people with major depression *[High Quality Evidence]*.

Screening (CAGE, CAGE-AID, Alcohol Use Disorders Identification Test [AUDIT], AUDIT—Consumption (AUDIT-C])

Current alcohol or other drug problems can be screened by asking a few questions that can be easily integrated into a clinical interview. The work group reviewed the literature on instruments designed to screen for substance use disorders.

CAGE and CAGE-AID. The CAGE questions are sensitive and specific for diagnosing alcoholism. One positive response has a sensitivity of 85% and a specificity of 89%, and two positive responses have a specificity of 96% *[Low Quality Evidence]*. The CAGE-AID questionnaire broadens the CAGE to include other drug use.

AUDIT and AUDIT-C. The AUDIT screening tool accurately detects alcohol dependency in depressed/anxious men and women; however, the overall performance of the AUDIT in detecting alcohol abuse is limited *[Low Quality Evidence]*. The AUDIT-C, a modified version of the 10 question AUDIT instrument, can help identify persons who are hazardous drinkers or have active alcohol use disorders.

Other instruments that were reviewed included Michigan Alcohol Screening Test (MAST), Short Michigan Alcohol Screening Test (SMAST), SMAST Adjusted to Include Drugs (AID) (SMAST-AID).

See Appendix G, "Alcohol Use Disorders Identification Test (AUDIT) Structured Interview," in the original guideline document.

See the original guideline document for examples of other substance abuse screening tools.

Treatment

The medical literature does not support definitive statements about the best way(s) to treat patients who are diagnosed with both major depression and substance abuse/dependence. Based on the majority of studies reviewed, success in treating dependency on alcohol, cocaine, and other abused substances is more likely if accompanying depression is addressed. Fewer investigators have looked at whether treating substance abuse is helpful in reducing depression. There is some evidence that patients with major depression that is secondary to their substance abuse may have remission of their depressed mood once the substance abuse is treated. However, it is difficult to separate secondary depression from primary depression that predates or is separate from the substance use.

Additional Resources. A complete discussion of evaluation and treatment for chemical dependency is beyond the scope of this guideline. However, SBIRT (Screening, Brief Intervention, Referral and Treatment) is a process wherein a care coordinator uses motivational interviewing to assist patients who have high-risk drinking behavior. Additionally, the National Institute on Alcohol Abuse and Alcoholism and other agencies offer tools to guide primary care-based medical treatment of alcohol abuse. See Web site links in the original guideline document.

Psychiatric Comorbidity

Bipolar Disorder

Be aware of ongoing mental illness diagnosis or other mental health illnesses and comorbidities. Patients with a history of manic (bipolar) symptoms now presenting with major depression may be destabilized if treated only with antidepressant drugs. If a manic or hypomanic episode occurs while treating a patient for depression, change the diagnosis to bipolar affective disorder and treat accordingly *[Low Quality Evidence]*. Behavioral health involvement is advised with these patients absent a prior history of successful primary care management.

Generalized Anxiety Disorder and Panic Disorder

Depressed patients may present with comorbid panic symptoms and generalized worries. Primary care clinicians should screen for symptoms of these disorders and potential causes. Assess for the following:

- Excessive use of stimulant containing products such as energy drinks or shots and caffeinated beverages
- Presence of medical causes of symptoms: thyroid disease, cardiac disease, irritable bowel syndrome, migraines, vestibular disorders, respiratory and pulmonary disorders
- Use of medications like psychostimulants
- Use of or withdrawal of substances like cocaine, methamphetamine, tetrahydrocannabinol (THC), or alcohol

Psychotherapy is an effective treatment for anxiety and panic, and a referral to a therapist who provides a short-term, evidence-based focused treatment protocol for anxiety is likely to be helpful. A comprehensive discussion of the treatment of anxiety disorders in primary care is beyond the scope of this guideline. However, the AHRQ's clinical practice guideline for the treatment of patients with anxiety disorders in primary care is a good reference point (Agency for Healthcare Research and Quality, 2008 *[Guideline]*.

Also see Annotation #8, "Comprehensive Treatment Plan with Shared Decision-Making," for medication and psychotherapy and integrative medicine treatments.

See the original guideline document for information on other disorders.

6. Additional Considerations (Medical Comorbidity, Cultural Considerations, Special Populations)?
   Recommendations:

   - Clinicians should assess and treat for depression in patients with some comorbidities *(Low Quality Evidence, Strong Recommendation)*.
   - Clinicians should acknowledge the impact of culture and cultural differences on physical and mental health *(Low Quality Evidence, Strong Recommendation)*.
   - When using pharmacotherapy in elderly patients, the clinician should carefully consider how the metabolism of the drug may be affected by physiologic changes, their comorbid illnesses and the medications used for them *(Low Quality Evidence, Strong*

Recommendation).

- Clinicians should screen and monitor depression in pregnant and postpartum women *(Low Quality Evidence, Strong Recommendation)*.

Medical Comorbidity

The importance of the interplay between depression and many medical comorbidities cannot be overstated. Depressed patients often have comorbid conditions. A long list of medical conditions has been associated with increased risk for depression; these include chronic pain, diabetes, cancer, human immunodeficiency virus (HIV), Parkinson's disease, cardiovascular and cerebrovascular disease, and multiple sclerosis, to name a few *[Low Quality Evidence]*. Undiagnosed or undertreated depression has been associated with worsened outcomes in cancer, cardiovascular disease, and other conditions *[Low Quality Evidence]*, *[Guideline]*. Conversely, one would expect that effective identification and treatment of comorbid depression would be associated with improved medical outcomes. Studies have demonstrated an association between effective treatment of depression and improved adherence to medical treatment for conditions such as cardiovascular disease *[Low Quality Evidence]*. However, other suspected benefits of antidepressant therapy, such as decreased mortality after myocardial infarction (MI) or coronary artery bypass graft (CABG), have been more difficult to prove. See "Implementation Tools and Resources Table" in the original guideline document for more information.

The following conditions are particularly important for screening, given the findings.

Cardiovascular Disease

Interplay of Risks

Some studies have shown that major depression is associated with an increased risk of developing coronary artery disease *[Systematic Review]*, and with an increased risk of mortality in patients after myocardial infarction by as much as fourfold *[Guideline]*, *[Low Quality Evidence]*, while other analyses have disputed this *[Low Quality Evidence]*, *[Systematic Review]*. Moderate to severe depression before CABG surgery and/or persistent depression after surgery increases the risk of death after CABG more than twofold higher than non-depressed patients *[Low Quality Evidence]*. Depression is three times more common in patients after acute myocardial infarction than in the general population and, notably, young women are at particularly high risk for depression after myocardial infarction *[Guideline]*.

Potential Explanations

Several possible mechanisms are proposed to explain why depression increases the risk of developing cardiovascular disease including behavioral issues such as increased smoking, obesity, sedentary lifestyle, and lack of adherence to medication.

Biologic phenomena associated with depression such as increased inflammatory processes (elevated C-reactive protein or cytokine levels), increased platelet dysfunction (heightened platelet aggregation or adhesiveness), and abnormalities in endothelial function may also explain possible mechanisms for an increased risk *[Low Quality Evidence]*.

Treating Depression in This Population

As yet there are no data to support the hypothesis that antidepressant treatment decreases cardiac morbidity and mortality *[Low Quality Evidence]*. Nevertheless, consensus opinion is to treat depressed cardiac patients with a safe drug rather than watchful waiting since they would benefit from symptomatic relief of their depressive symptoms and there is a potential improvement in their cardiovascular risk profile *[Low Quality Evidence]*.

Although tricyclic antidepressants are effective against depression, they are associated with cardiovascular side effects including orthostatic hypotension, slowed cardiac conduction, proarrhythmic activity, and increased heart rate. Selective serotonin reuptake inhibitors (SSRIs), by contrast, are well tolerated and have a more benign cardiovascular profile; they would be preferred initial agents for treatment of depression in individuals with cardiovascular disease *[Low Quality Evidence]*. The recent American Heart Association science advisory *[Guideline]* suggests sertraline and citalopram as first-line drugs for patients with coronary heart disease.

See Annotation #8, "Comprehensive Treatment Plan, with Shared Decision-Making" section: SSRIs and other anti-depressants.

For more information, see also the NGC summaries of the ICSI guidelines Heart Failure in Adults and Stable Coronary Artery Disease.

Cerebrovascular Disease

A recent meta-analysis *[Systematic Review]* affirms earlier findings *[Low Quality Evidence]*, *[Systematic Review]* of an association between depression and stroke. The pooled hazard ratio from the meta-analysis was 1.45, on par with the association between smoking and stroke, and obesity and stroke. The authors suggest potential causative mechanisms similar to those discussed above for cardiovascular

disease. They also suggest the need for further studies to assess the "role of depression treatment in modulating subsequent risk of stroke."

Diabetes

Major depression is associated with an increased number of known cardiac risk factors in patients with diabetes and a higher incidence of coronary heart disease; therefore, screening and treatment of depression in this patient group should be emphasized *[Low Quality Evidence]*.

Individuals with diabetes have twofold higher odds of depression than those without diabetes. High levels of symptoms associated with diabetes that do not correlate with physical or laboratory assessments should prompt the physician to assess for depression *[Low Quality Evidence]*.

Depression earlier in life increases the risk of developing diabetes by twofold *[Low Quality Evidence]*.

Depressive symptom severity is associated with poorer diet, medication compliance, and self-care plus functional impairment and higher health care costs *[Low Quality Evidence]*.

For more information, see also the NGC summary of the ICSI guideline Diagnosis and Management of Type 2 Diabetes Mellitus in Adults.

Chronic Pain

Depression and pain symptoms commonly coexist, exacerbate, or attenuate one another, and appear to share biological pathways and neurotransmitters (see the original guideline document for information on important diagnostic and treatment findings regarding chronic pain).

Key Clinical Practice Actions

- In those patients presenting with either pain or depressive symptoms, assess both domains. Depression may be more than a facet of chronic pain when significant depression symptoms are present. If comorbidity is found between chronic pain and mild to moderate major depression, treat both conditions for optimal outcomes *[Low Quality Evidence]*. If comorbid severe major depressive disorder is diagnosed concurrently with chronic pain, depressive symptoms should be the primary focus of treatment.
- Depression and pain symptoms appear to follow the same descending pathways of the central nervous system involving a functional deficiency of the neurotransmitters serotonin, norepinephrine, and dopamine. Therefore, antidepressant medication is warranted, especially the dual-action tricyclic antidepressants such as amitriptyline or dual action atypical antidepressant reuptake inhibitors such as venlafaxine or duloxetine. Duloxetine is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy *[High Quality Evidence]*.
- Combining pharmacologic treatment and cognitive-behavioral therapy appears to produce the most favorable treatment outcomes *[Low Quality Evidence]*.

For more information, see also the NGC summary of the ICSI guideline Assessment and Management of Chronic Pain.

Cultural Considerations

Successful care is most likely to occur when the clinician:

- Uses appreciative inquiry by asking questions that produce positive potential and strengths
- Regards the patient's cultural norms and beliefs
- Uses interpreters whenever possible
- Seeks to incorporate the patient's beliefs into the treatment plan

A person's cultural and personal experiences influence his/her beliefs and therefore attitudes and preferences. If these experiences are taken into consideration, openness to and readiness to change (including readiness to seek and adhere to treatment) will be enhanced. People of differing racial/ethnic groups are successfully treated using currently available evidence-based interventions when differential personal elements, from biological to environmental to cultural, are considered during the treatment planning process *[Low Quality Evidence]*.

Online resources including http://www.culturecareconnection.org and http://minorityhealth.hhs.gov have readily available information and facts. See the "Implementation Tools and Resources" section in the original guideline document for more information.

See the original guideline document for information about cultural considerations regarding cultural beliefs and common presentations, ethnic minority women, African Americans, Latinos/Hispanics, Asians, psychosocial and socioeconomic issues, and assessment and treatment tools.

Special Populations

See the original guideline document for a discussion of special populations, including geriatrics, dementia/cognitive impairment, and pregnant and postpartum women.

7. Address Secondary Causes and/or Adapt a Plan for the Special Population
People with secondary causes for major depression may also have an underlying primary mood or anxiety disorder. Understanding and addressing nuances of special populations may enhance treatment outcomes. See Annotation #5, "Assess for the Presence of Substance Abuse or Psychiatric Comorbidity If Suspected" and Annotation #6, "Additional Considerations (Medical Comorbidity, Cultural Considerations, Special Populations)?"

8. Comprehensive Treatment Plan with Shared Decision-Making
Recommendations:

- A collaborative care approach is recommended for patients with depression in primary care *(High Quality Evidence, Strong Recommendation)*.
- A written and mutually agreed-upon treatment plan engaging the patient and family is recommended *(Low Quality Evidence, Strong Recommendation)*.
- Clinicians should discuss the spectrum of treatment options. These options include antidepressant medications and/or psychotherapy treatments and integrative medicine treatments *(Low Quality Evidence, Strong Recommendation)*.
- Clinicians should establish and maintain follow-up with patients *(Low Quality Evidence, Strong Recommendation)*.

Collaborative Care Model

Strong Evidence

More than 37 randomized controlled trials have demonstrated the effectiveness of the collaborative care model, in which primary care treatment of depression is provided by a team (depression care manager, primary physician, consulting psychiatrist, others). The work group recommends three key references (see the original guideline document *[Meta-analysis]*, *[High Quality Evidence]*). This model has demonstrated improvement in treatment adherence, patient quality of life, and depression outcomes. Beneficial impact on direct medical costs can also be found. Further dissemination of this model has been recommended *[Low Quality Evidence]*. Preliminary evidence suggests the collaborative care model is also effective for depression during pregnancy and postpartum *[Low Quality Evidence]*.

Improved Patient Outcomes

Better medication compliance and reduced risk of relapse. The use of a collaborative care model can help with medication compliance, by providing closer follow-up than is possible without a care manager. Three or more follow-up visits in the first three months reduced the risk of relapse/recurrence of depression, as did continuous use of antidepressants *[Low Quality Evidence]*. Care management facilitates continuous use of antidepressants, by providing close follow-up and early intervention when side effects occur.

Implementing a Collaborative Care Approach

Design. The design of a team-based collaborative care approach *[High Quality Evidence]* involves:

- Primary care providers using evidence-based approaches to depression care and a standard tool for measuring severity, response to treatment plan and remission
- A systematic way of tracking and reminding patients at appropriate intervals of visits with their primary care physician and monitoring of treatment adherence and effectiveness
- A team member (care manager role) to utilize the tracking system and make frequent contacts with the patients to provide further education, self-management support, and monitor for response in order to aid in facilitating treatment changes and in relapse prevention
- Communication between primary care team and psychiatry to consult frequently and regularly regarding patient under clinical supervision, as well as direct patient visits as needed

Challenges. There are challenges in providing the collaborative care model that need to be acknowledged and addressed by the health care organization. Some of these challenges include:

- Identifying depressed patients in the practice
- Identifying the desired background experience for care managers
- Establishing the responsibilities and scope of practice of the care managers
- Locating the care managers (centrally versus clinic-based)

- Deciding on type of care manager interaction with patients (telephonic versus face-to-face)
- Determining level of supervision by psychiatrists
- Seeking adequate reimbursement for services provided to ensure program sustainability

[Low Quality Evidence]

See the "Implementation Recommendations" (in the "Description of Implementation Strategy" field of this summary) and the "Implementation Tools and Resources Table" section of the original guideline document for suggestions and information on implementing the collaborative care model.

Educate and Engage Patient

Successful care of major depression as an illness requires active engagement of each patient and his/her family, plus ongoing patient education, beginning at the time of diagnosis.

Often, the depressed patient's pessimism, low motivation, low energy, and sense of social isolation and guilt may lead to nonadherence with treatment *[Guideline]*.

Topics to cover: Education topics should include:

- The cause, symptoms and natural history of major depression
- Treatment options and the process of finding the best fit for a given individual
- Information on what to expect during the course of treatment
- How to monitor symptoms and side effects
- Follow-up protocol (office visits and/or telephone contacts)
- Early warning signs of relapse or recurrence
- Length of treatment
- Communication with the caregiver

A patient should plan to make appointments for six months to one year. Frequency of visits will depend on depression severity. See "Establish Follow-Up Plan" further in this annotation.

Patient education should include diagnosis, prognosis, and treatment options including costs, duration, side effects, and expected benefits.

While the clinician goal of the PHQ-2 and PHQ-9 is detecting and diagnosing depression, these tools are, in real-world use, often used primarily in shared decision-making with patients to "suggest, tell, or convince patients to accept the diagnosis of depression" *[Low Quality Evidence]*.

Support and education in the primary care setting are critical and contribute to the likelihood of good follow-through on treatment. It may help patients understand their options and resources if the primary care clinic explains that the support-plus-education component of treatment is not the same as a course of psychotherapy. Clinic staff may also want to identify a family member or support person of the patient's choosing and establish their role within the patient's treatment plan.

Key messages for patients and families: Emphasize the following points:

- Depression is a medical illness, not a character defect.
- Treatment is effective for most patients.
- The aim of treatment is remission – being predominately free of symptoms.
- Relapse prevention is a key aspect of management – not just getting better, but also staying well. The risk of recurrence is significant: 50% after one episode, 70% after two episodes, 90% after three episodes *[Low Quality Evidence]*. Patient and family should be alert to early signs and symptoms of recurrence and seek treatment early if depression returns.

People of differing racial/ethnic groups can be successfully treated using currently available evidence-based interventions as long as distinctive personal elements, from biological to environmental to cultural, are considered during the treatment planning process *[Low Quality Evidence]*.

Patient Engagement

Three broad types of patient engagement strategies have high-quality evidence supporting their use and documenting positive impacts: 1) patient self-management, 2) behavioral activation and 3) appropriate physical activity.

Patient Self-Management

It is important for the patient to consider and adopt some self-care responsibilities. These responsibilities may range from simply demonstrating reliable behavior in taking medications and notifying the clinician about side effects to agreeing to participate in sessions, or journaling and completing homework, which is necessary for some cognitive behavioral therapies. Written materials are helpful to reinforce information shared during the discussion. Bibliotherapy, a therapy approach wherein the patient is encouraged to read self-help books and other relevant materials, has modest empirical support for benefiting patients who are motivated to augment their professional care with self-help literature *[Meta-analysis]*.

See the "Implementation Tools and Resources Table" section of the original guideline document for examples of book titles.

Behavioral Activation — Scheduled Pleasant Activities

Activity scheduling is a straightforward behavioral intervention in which patients are taught to increase their daily involvement in pleasant activities and to increase their positive interactions with the environment *[Low Quality Evidence]*. This is an attractive intervention for the treatment of depression because it is simple in concept, easily taught, and efficient. In addition, behavioral activation does not require complex skills on the part of either patient or clinician.

The relative simplicity of encouraging patients to increase their daily participation in pleasant activities makes activity scheduling an attractive treatment approach for individuals who may be difficult to treat, such as depressed dementia patients or depressed elderly patients. Regular outings and get-togethers, participation in a senior day care program, participation in available nursing home activities, etc., are all likely to reduce depression in the elderly *[Meta-analysis]*.

Appropriate Physical Activity

Evidence suggests that physical activity at a dose consistent with public health recommendations is a useful tool for easing major depression symptoms *[High Quality Evidence]*. Exercise has been shown to work well as monotherapy or adjuvant to medication in moderate depression. Exercise has shown promise as adjuvant therapy in treatment-resistant major depression in women, and there is a small but growing body of evidence of some long-term as well as preventive attributes *[High Quality Evidence]*.

When prescribing exercise either alone or as an adjunct to medication and psychotherapy, the complexity and the individual circumstances of each patient must be considered. When prescribing an exercise prescription, several caveats apply:

- Anticipate barriers. Hopelessness and fatigue can make physical exertion difficult.
- Keep expectations realistic. Some patients are vulnerable to guilt and self-blame if they fail to carry out the regime.
- Introduce a feasible plan. Walking, alone or in a group, is often a good option.
- Accentuate pleasurable aspects. The specific choice of exercise should be guided by the patient's preferences, and must be pleasurable.
- Encourage adherence. Greater antidepressant effects are seen when training continues beyond 16 weeks.
- A goal of 30 minutes of moderate-intensity aerobic exercise, three to five days a week is recommended for otherwise healthy adults (17.5 kcal/kg/week of total energy expenditure). For more information see the NGC summary of the ICSI guideline Prevention and Management of Obesity for Adults.

Discuss Treatment Options

Primary goal. When considering treatment options, the primary goal is to achieve remission or to get the patient to be predominately symptom-free (i.e., a PHQ-9 score of less than five *[Low Quality Evidence]* or a Hamilton Rating Scale for Depression [HAMD]-17 score of less than or equal to 7 *[Low Quality Evidence]*).

Shared decision-making. Shared decision-making is a practice that guides patients, families, and physicians through a reliable process that incorporates patient values, priorities, and goals into discussions of risks and benefits of treatment options *[Systematic Review]*. Central aspects of the patient-physician partnership include exploring antidepressant concerns, working with treatment preferences, and providing continued supportive management. There is at present a lack of good quality research evidence about the long-term effects of shared decision-making interventions in mental health conditions *[Systematic Review]*. A mismatch between patients' preferred and prescribed treatment acts as a significant barrier to sustained adherence *[Low Quality Evidence]*. Patient participation in shared treatment decision-making improves depression treatment adherence and clinical outcomes in depressed patients *[Low Quality Evidence]*.

Psychotherapy and Pharmacotherapy

Presentation influences choice. If the initial presentation is mild to moderate, either an antidepressant or psychotherapy (or both) is indicated. If the presenting symptoms of depression are severe or chronic, the initial recommendation is to treat with antidepressants and psychotherapy. See the table "Translating PHQ-9 Depression Scores into Practice Based on DMS-5 Criteria" below.

In mild to moderate levels of depression, psychotherapy can be equally as effective as medication *[High Quality Evidence]*. With severe depression, antidepressant medication may be necessary *[High Quality Evidence]*. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, cognitive behavioral therapy (CBT) had equal efficacy to the addition of another antidepressant medication, or to the switching of antidepressant medication, when the patient had not responded to the initial medication *[Low Quality Evidence]*. If the patient presents with comorbid anxiety and initial pharmacological treatment does not work, refer patient for anxiety-based CBT for anxious depression and behavioral activation *[Low Quality Evidence]*.

Factors to consider in making treatment recommendations. Consider symptom severity and chronicity, presence of psychosocial stressors, presence of comorbid conditions, cultural/health beliefs, resource accessibility and sufficiency, and patient preferences. Patients who perceive more self-control of their health experience greater reduction in depressive symptoms, whether treated with psychotherapy or an antidepressant *[Low Quality Evidence]*. Results from a systematic review found clinical benefits when racial and ethnic minority female patients were allowed to choose their treatment (medication, psychotherapy or both) and were provided support and outreach services *[Systematic Review]*. Because both antidepressants and psychotherapy are effective, careful consideration of patient preference for mode of treatment is appropriate *[High Quality Evidence]*. (See the table "Translating PHQ-9 Depression Scores into Practice Based on DMS-5 Criteria" below, and Annotation #6, "Additional Considerations (Medical Comorbidity, Cultural Considerations, Special Populations)?"

Psychotherapy

As with all depression treatment, the goal of psychotherapy is to reach remission and prevent or minimize relapse. Offer a referral for psychotherapy whenever psychological or psychosocial issues are prominent, or if the patient requests it.

Documented effectiveness. CBT, interpersonal therapy (IPT), short-term psychodynamic psychotherapy (STPP) and problem-solving treatment (PST) have documented efficacy *[Systematic Review]*, *[Meta-analysis]*, *[Low Quality Evidence]*, *[High Quality Evidence]*. Early research on Internet-delivered psychotherapy for depression in adults is also promising *[Low Quality Evidence]*. Mindfulness-based therapies have been demonstrated as effective in reducing symptoms of anxiety and depression, and in reducing the incidence of relapse in depression *[Low Quality Evidence]*, *[Meta- analysis]*, *[Systematic Review]*. Early research on protocolized computer-based CBT for depression in adults is also promising *[Low Quality Evidence]*. There is now significant evidence that psychotherapy plus medication is better than medication alone for moderate to severe unipolar depression *[Meta-analysis]*. In primary care settings, brief CBT and PST (defined as eight or fewer sessions) were effective treatments for the acute phase of depression and demonstrated modest effect sizes comparable to antidepressant medication and standard duration psychotherapy treatments *[Systematic Review]*. Psychotherapy, especially focused psychotherapy, can significantly reduce symptoms, restore psychosocial and occupational functioning, and prevent relapse in patients with major depression *[Meta-analysis]*. Maintenance psychotherapy is useful in managing chronic forms of major depressive disorder *[High Quality Evidence]*. Evidence-based psychotherapy for depression does not specifically address treatment where there is comorbid anxiety.

Following up is essential. If the patient is newly involved in psychotherapy, the following are important:

- Contact with patient in 4 to 6 weeks
- Communicate with therapist in 4 to 6 weeks
- Return visit in 8 to 10 weeks to evaluate progress
- Communicate to the patient that it can take 8 to 10 weeks of regular and frequent therapy to show improvement

Integrative Medicine

Mindfulness-based Stress Reduction

Mindfulness-based stress reduction (MBSR) is a structured group program based on use of mindfulness meditation to reduce suffering associated with physical, psychosomatic and psychiatric disorders. It has received much attention since 2000 and has been found to be effective in reducing symptoms of depression and risk of relapse *[Meta-analysis]*.

Acupuncture and Yoga

Existing meta-analyses and systematic reviews vary with respect to acupuncture protocol (manual, electroacupuncture or sham), methodological soundness and efficacy results *[Systematic Review]*. Both sham and active acupuncture participants generally report symptomatic depression improvement *[Systematic Review]*. Serious adverse events from acupuncture are very uncommon, which may appeal to those who seek to avoid side effects associated with traditional treatments (e.g., medication side effects). Rigorous positive studies are needed before acupuncture can be recommended for the treatment of major depressive disorder.

Acupuncture and yoga are both effective as adjunctive treatment to decrease severity of symptoms *[Guideline]*.

Herbals and Dietary Supplements

Caution: Many drugs interact with St. John's wort, including other antidepressants, warfarin, oral contraceptives, antiretroviral, anti-cancer and anti-rejection drugs. Care should be taken to ask all patients what medications they are taking, including over-the-counter and supplements, to avoid these interactions.

Herbal products and nutritional supplements are not evaluated or regulated by the U.S. Food and Drug Administration (FDA) for safety, efficacy, or bioavailability.

St. John's Wort and Sam-E. In a meta-analysis *[Systematic Review]*, S-adenosylmethionine (Sam-E) and hypericum perforatum (St. John's wort) were found to have indications for mild to moderate depression but not major depression. Sam-E and St. John's wort should not be taken in combination with other antidepressant medications.

A Cochrane meta-analysis concluded that there is insufficient evidence to recommend the use of acupuncture or St. John's wort in the treatment of major depression. Research is limited by lack of large scale randomized controlled trials (RCTs)

Omega-3 fatty acid (FA) not helpful as treatment. A recent meta-analysis of randomized, placebo-controlled trials of omega-3 FA in the treatment of major depressive disorder demonstrated no significant benefit of omega-3 FA treatment compared to placebo and significant heterogeneity in study design, as well as publication bias *[Systematic Review]*.

Refer to the original guideline document for information on possible link between deficiency and depression, omega-3 FA, and vitamin D.

Medications

The acute treatment phase is focused on treating the patient to remission. Acute therapy typically lasts 6 to 12 weeks but technically lasts until remission is reached *[Guideline]*. Full remission is defined as a two-month period devoid of major depressive signs and symptoms.

Adherence, Patient Interaction and Monitoring

Adherence is paramount. For antidepressant medications, adherence to a therapeutic dose and meeting clinical goals are more important than the specific drug selected. Successful treatment often involves dosage adjustments and/or trial of a different medication at some point, to maximize response and minimize side effects *[Guideline]*.

Key messages for patients using antidepressant therapy. When antidepressant therapy is prescribed, the following key messages should be highlighted to support medication adherence and completion:

- Side effects from medication often precede therapeutic benefit and typically recede over time. It is important to expect some discomfort prior to the benefit.
- Successful treatment often involves dosage adjustments and/or trial of a different medication at some point, to maximize response and minimize side effects.
- Most people need to be on medication at least 6 to 12 months after adequate response to symptoms.
- Patients may show improvement at two weeks but need a longer length of time to really see response and remission.
- Take the medication as prescribed, even after you feel better. Premature discontinuation of antidepressant treatment has been associated with a 77% increase in the risk of relapse/recurrence of symptoms *[Low Quality Evidence]*. The probability of recurrence of depressive symptoms was found to be 25% after one year, 42% after two years, and 60% after five years in one study *[Low Quality Evidence]*. Each episode of recurrence increased the risk of subsequent episodes by 16% *[Low Quality Evidence]*.
- Do not stop taking the medication without calling your clinician. Side effects can be managed by changes in the dosage or dosage schedule.

Adherence strategies. Consider increasing education, engagement, and follow-up for patients who are at higher risk for not adhering to treatment. For antidepressant treatment this includes patients who are newly diagnosed with depression, in the midst of their first depression, or who have lapsed in the middle of a previous course of treatment *[Low Quality Evidence]*. In addition to medication monitoring, clinical management of patients placed on antidepressants should include the clinician's support and reassurance.

Risks for children, adolescents and young adults. The FDA has requested manufacturers of antidepressants include a warning statement regarding antidepressants increasing the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults. The full warning statement can be found at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273 . FDA-approved medication guides are required to be distributed to patients who receive antidepressants. A complete list of specific medication guides can be found at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273 .

Be alert for worsening of symptoms. Health care clinicians should carefully evaluate their patients in whom depression persistently worsens, or emergent suicidality is severe, abrupt in onset, or was not part of the presenting symptoms. Reassessment is required to determine what intervention, including discontinuing or modifying the current drug therapy, is indicated.

The clinician should instruct the patient and the patient's caregiver to be alert for the emergence of agitation, irritability, and other symptoms. The emergence of suicidality and worsening depression should be closely monitored and reported immediately to the clinician.

See also Annotation #4, "Is Patient Unsafe to Self or Others?" above.

Selection of an Antidepressant Medication

The effectiveness of antidepressant medications is generally comparable between classes and within classes of medications *[Guideline]*. However, there are distinct differences inside effects caused by the classes of medications and individual agents.

Antidepressant drug selection should be based on:

- The patient's and family history of response to previous antidepressant medications (if any)
- Clinician experience with specific antidepressants
- Patient preferences
- Side effect profile (e.g., sedating, activating, weight gain, impact on sex life). Antidepressant medications with anticholinergic side effects contribute to dry mouth/xerostomia, caries, gingivitis, and periodontal disease *[Low Quality Evidence]*. This risk should be discussed with patients prior to initiation of these medications.
- Safety in overdose (e.g., ten days of a tricyclic antidepressant [TCA] can be a lethal overdose)
- Availability and costs
- Drug-drug interactions
- Positive or negative impacts on the patient's comorbid psychiatric or medical conditions (for example, smoking cessation, attention deficit hyperactivity disorder [ADHD])
    - Anxiety
      The good news for the primary care clinician is that there is a great deal of overlap between effective pharmacotherapy for major depression, panic disorder, and generalized anxiety disorder. Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and TCAs demonstrate efficacy in numerous controlled trials *[Guideline]*. The favorable safety and side effect profiles of SSRIs and SNRIs make them natural first considerations for treating comorbid anxiety disorders. While similarly efficacious, TCAs introduce greater risk in overdose and potential side effects. With all antidepressant medications used to treat anxiety, consider a lower initial starting dose due to potential increased sensitivity to side effects in patients with panic and generalized anxiety disorders. Once the patient tolerates the lower starting dose, advance the dose gradually to a therapeutic and tolerable dose to minimize partial response and non-response *[Guideline]*. For further discussion of assessment and treatment for anxiety, see Annotation #5, "Assess for the Presence of Substance Abuse or Psychiatric Comorbidity If Suspected."

    - Panic Disorder
      Evidence supports benzodiazepine use in panic disorder treatment *[Guideline]*. The work group encourages cautious and limited use due to risk for dependence and abuse. Benzodiazepines can be an effective means to manage more severe panic symptoms early in the initiation of other therapy (e.g., antidepressant or psychotherapy) or with acute exacerbation of anxious symptoms. If used, a scheduled course of a longer-acting benzodiazepine, such a clonazepam, is recommended over a shorter-acting benzodiazepine, such as alprazolam.

      Just as in the management of major depression, close initial follow-up is advised to gauge response to therapy. Additional medication options include use of or augmentation with mirtazapine, gabapentin or pindolol. The evidence for the use of these is less robust than for the medications above *[Low Quality Evidence]*, *[Guideline]*.

    - Insomnia
      When selecting an antidepressant in a patient whose symptoms include insomnia, consider prescribing a sedating antidepressant (e.g., trazodone, mirtazapine). If acute relief is needed, consider a benzodiazepine for short-term usage, but it is not recommended for long-term use. Also consider selective gamma-aminobutyric acid (GABA) agonist hypnotic (e.g., zolpidem, eszopiclone). The most common side effect of mirtazapine is sedation. It may be prescribed for depressed patients with initial insomnia and given at bedtime.

The Texas Medication Algorithm Project (TMAP) provides good overall parameters for care. See the "Implementation Tools and

Resources Table" in the original guideline for more information. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study has updated data on treatment response timelines and follow-ups.

There is no evidence regarding choice of brand versus generic based on adverse clinical outcomes.

While genetic differences in the metabolism of certain medications including antidepressants can be determined by genetic testing, the clinical significance and applicability to practice has not yet been established.

For up-to-date prescribing information, the work group recommends the following references:

- The Physician's Desk Reference: http://www.pdr.net
- The American Hospital Formulary Service (AHFS): http://ashp.org/ahfs
- Micromedex: http://www.micromedex.com
- Epocrates: http://www.epocrates.com

Consider discussing with the patient the specific side effect profiles, costs, and benefits of different antidepressants, including generics. Cost implications for patients need to be discussed between provider and patient.

Selective Serotonin Reuptake Inhibitors and Other Antidepressants

SSRIs — as well as venlafaxine, duloxetine, desvenlafaxine, mirtazapine and bupropion — are frequently recommended as first-line antidepressant treatment options due to the quality and quantity of published data, and relative tolerability of side effects compared to TCAs and monoamine oxidase inhibitors (MAOIs) and their overall relative safety *[Guideline]*, *[Low Quality Evidence]*. They generally lack the common adverse reactions (anticholinergic, sedative effects) of the tricyclics and cause fewer problems when taken in overdose. However, they may cause headache, nervousness, insomnia, and sexual side effects. They may also be more expensive because some may not yet be available as generics.

Citalopram Warning

In 2011, the FDA published a "Medwatch" drug safety alert regarding the potential risk of abnormal heart rhythms associated with citalopram doses greater than 40 mg a day due to concerns about prolonged QT interval prolongation and the risk for torsades de pointes. Prescribers were initially told to avoid using citalopram doses higher than 40 mg and discouraged from using it at all in patients with congenital long QT syndrome, bradyarrhythmias, congestive heart failure, or at risk for developing hypokalemia or hypomagnesemia. In March 2012 this was revised by downgrading the warning from "contraindicated" to "not recommended" for patients with congenital long QT syndrome because patients with this condition have few viable alternative treatments. Ongoing monitoring was suggested, a maximum dose of 20 mg/day was recommended for age >60, and discontinuation was recommended when QTc >500ms.

A recent review of Veterans Health Administration patients who were prescribed citalopram between 2004 and 2009 (N=618,450) found daily doses of citalopram greater than 40 mg a day were associated with lower risks of ventricular arrhythmias, all-cause mortality, and non-cardiac mortality, compared with lower doses of citalopram. Overall, no increased risks of cardiac mortality were observed. These results were similar when compared with a cohort of patients prescribed sertraline (N=365,898) during the same time period.

Secondary Amine Tricyclics

The literature clearly supports the effectiveness of tricyclics. Because of associated side effects, TCAs are used less frequently as first-line agents.

Secondary (nortriptyline) amine tricyclics cause less orthostatic hypotension and sedation than do tertiary (amitriptyline) amine tricyclics.

These medications should be monitored cautiously in patients with heart problems, or in patients with potential for drug interactions. Monitoring blood levels and electrocardiogram (EKG) may be advised.

Monoamine Oxidase Inhibitors (MAOIs)

MAOIs, in general, should be restricted for patients who do not respond to other treatments because of their potential for serious side effects and the necessity of dietary restrictions. Patients who have major depressive disorders with atypical features are one group for whom several studies suggest MAOIs may be particularly effective. However, in clinical practice, many psychiatrists start with SSRIs in such patients because of the more favorable adverse effect profile. Consider a dietary and/or psychiatry consult if prescribing MAOIs.

Atypical Antipsychotics

There is some evidence regarding the use of quetiapine as monotherapy for the treatment of major depression *[Systematic Review]*.

See the original guideline document for information on serotonin syndrome, medication interactions with antidepressant agents, and consideration of antidepressants in elderly patients.

Establish Follow-Up Plan

Proactive follow-up contacts (in person, telephone) based on the collaborative care model have been shown to significantly lower depression severity *[High Quality Evidence]*. In the available clinical effectiveness trials conducted in real clinical practice settings, even the addition of a care manager leads to modest remission rates *[High Quality Evidence]*. Interventions are critical to educating the patient regarding the importance of preventing relapse, safety and efficacy of medications and management of potential side effects. Establish and maintain initial follow-up contact intervals (office, phone, other) *[High Quality Evidence]*.

The PHQ-9 is an effective management tool. The PHQ-9 is an effective management tool, as well, and should be used routinely for subsequent visits to monitor treatment outcomes and severity. It can also help the clinician decide if/how to modify the treatment plan *[Low Quality Evidence]*. Using a measurement-based approach to depression care, PHQ-9 results and side effect evaluation should be combined with treatment algorithms to drive patients towards remission. A five-point drop in PHQ-9 score is considered the minimally clinical significant difference *[Low Quality Evidence]*.

Table. Translating Patient Health Questionnaire, 9-Item (PHQ-9) Depression Scores into Practice based on DSM-5 Criteria

PHQ-9 Symptoms and Impairment	PHQ-9 Severity	Intensity	Treatment Recommendations (for treatment durations, see also Annotation #10)
1 to 4 symptoms, minimal functional impairment	5-9	Subclinical	• Education to call if deteriorates • Physical activity • Behavioral activation • If no improvement after one or more months, consider referral to behavioral health for evaluation • Consider for persistent depressive disorder*
2 symptoms, #1 or #2 >0 score 2+, functional impairment	10-14	Mild Major Depression	• Pharmacotherapy or psychotherapy, or both • Education • Physical activity • Behavioral activation • Initially consider weekly contacts to ensure adequate engagement, then at least monthly
≥3 symptoms, #1 or #2 >0 score 2 +, functional impairment	15-19	Moderate Major Depression	• Pharmacotherapy, psychotherapy, or both • Education • Physical activity • Behavioral activation • Initially consider weekly contacts to ensure adequate engagement, then minimum every 2-4 weeks
≥4 symptoms, question #1 or #2 >0 score 2 +, marked functional impairment, motor agitation	≥20	Severe Major Depression	• Pharmacotherapy necessary and psychotherapy when patient is able to participate • Education • Physical activity • Behavioral activation • Weekly contacts until less severe

This table is designed to translate the PHQ-9 scores into DSM-5 categories and then integrate evidence-based best practice. It does not directly correspond to the PHQ-9 Scoring Guide in Appendix A, "Patient Health Questionnaire (PHQ-9)," of the original guideline document.

[Meta-analysis], *[Low Quality Evidence]*, *[Systematic Review]*

*Persistent depressive disorder is defined as low-level depression most of the day for more days than not for at least two years. Must include presence of at least two of the listed DSM-5 criteria affecting appetite, sleep, fatigue, self-esteem, concentration/decision-making or hopelessness). Initiate pharmacotherapy or refer to mental health specialty clinician for evaluation, or both. See also Annotation #2, "Diagnose and Characterize Major Depression with Clinical Interview."

Referral or co-management with mental health specialty clinician if patient has:

High suicide risk
Inadequate treatment response
Other psychiatric disorders such as bipolar, substance abuse, etc.
Complex psychosocial needs

If the primary care clinician is seeing some improvement, continue working with that patient to increase medication dosage or augment with psychotherapy or medication to reach remission. This can take up to three months. Don't give up on the patient whether treating in primary care or referring. Stay connected through consultation or collaboration and take the steps needed to get the patient to remission. This can take longer and can take several medication interventions or other steps. The STAR*D study has shown that primary care can be just as successful as specialty care *[High Quality Evidence]*.

Relapse Prevention

The prevention of relapse is of primary importance in the treatment of major depression. From 50% to 85% of people who suffer an episode of major depression will have a recurrence, usually within two or three years. Patients who have had three or more episodes of major depression are at 90% risk of having another episode. Relapse prevention interventions resulted in 13.9 additional depression-free days during a 12-month period *[High Quality Evidence]*.

Focused psychotherapy through cognitive-behavioral therapy can reduce relapse by assisting patients with their depression-related beliefs *[High Quality Evidence]*. In addition, focused psychotherapy can significantly reduce symptoms and restore psychosocial and occupational functioning in patients with major depression *[Meta-analysis]*.

Collaboration with Mental Health

Consider collaborating with a behavioral health care clinician for the following:

- Patient request for psychotherapy
- Presence of severe symptoms and impairment in patient, or high suicide risk
- Presence of other psychiatric condition (e.g., personality disorder, history of mania)
- Suspicion or history of substance abuse
- Clinician discomfort with the case
- Medication advice (psychiatrist or other mental health prescriber)
- Patient request for more specialized treatment

9. Is Patient Responding Adequately?
The goals of treatment should be to achieve remission, reduce relapse and recurrence, and return to previous level of occupational and psychosocial function.

Remission is defined as the absence of depressive symptoms, or the presence of minimal depressive symptoms such as HAM-D score of less than 7 or a PHQ-9 score of less than 5.

Response is defined as a 50% or greater reduction in symptoms (as measured on a standardized rating scale). Partial response is defined as a 25% to 50% reduction in symptoms.

Response and remission take time. In the STAR*D study, longer times than expected were needed to reach response or remission. In fact, one-third of those who ultimately responded did so after six weeks. Of those who achieved Quick Inventory of Depressive Symptomatology (QIDS) remission, 50% did so only at or after six weeks of treatment *[High Quality Evidence]*. If primary care clinician is seeing some improvement, continue working with that patient to augment or increase dosage to reach remission. This can take up to three months.

A reasonable criterion for extending the initial treatment: assess whether the patient is experiencing a 25% or greater reduction in baseline

symptom severity at six weeks of therapeutic dose. If the patient's symptoms are reduced by 25% or more, but the patient is not yet at remission, and if medication has been well tolerated, continue to prescribe. Raising the dose is recommended *[High Quality Evidence]*. Improvement with psychotherapy is often a bit slower than with pharmacotherapy. A decision regarding progress with psychotherapy and the need to change or augment this type of treatment may require 8 to 10 weeks before evaluation *[Low Quality Evidence]*.

10. Continuation and Maintenance Treatment Duration Based on Episode
Cognitive therapy and behavioral activation. Skill building and self-management practices learned through behavioral activation – plus other beneficial cognitive, behavioral, social, and exercise activities – are recommended for continuation and maintenance of depression treatment *[Meta-analysis]*, *[High Quality Evidence]*, *[Systematic Review]*. Recent studies demonstrate an enduring benefit of cognitive therapy and behavioral activation comparable to maintenance pharmacotherapy in reducing major depressive episode relapse and recurrence beyond one year of treatment *[High Quality Evidence]*.

Patients withdrawn from cognitive therapy were significantly less likely to relapse compared to patients withdrawn from pharmacotherapy; furthermore, those withdrawn from cognitive therapy were no more likely to relapse than those who continued pharmacotherapy *[High Quality Evidence]*. For patients who reached remission but had periodic depressive symptoms (defined as unstable remission), mindfulness based cognitive therapy or continuation pharmacotherapy significantly reduced depression relapse and recurrence rates *[High Quality Evidence]*.

Acute therapy is the treatment phase focused on treating the patient to remission. Acute therapy typically lasts 6 to 12 weeks but technically lasts until remission is reached *[Guideline]*. Full remission is defined as a two-month period devoid of major depressive signs and symptoms *[Guideline]*.

Continuation therapy is the 4-to-9 month period beyond the acute treatment phase during which the patient is treated with antidepressants, psychotherapy, electroconvulsive therapy (ECT), or other somatic therapies to prevent relapse *[Guideline]*. Relapse is common within the first six months following remission from an acute depressive episode; as many as 20% to 85% may relapse *[Guideline]*.

Maintenance therapy is the treatment phase that follows continuation therapy. The goal of maintenance therapy is to prevent recurrence of new or future episodes of major depression *[Low Quality Evidence]*. The best candidates for maintenance therapy are patients who meet any of these criteria:

- Three or more previous episodes of major depression
- Two episodes of major depression and rapid recurrence of episodes
- Older in age at the onset of major depression (more than 60 years of age)
- Severe episodes of major depression, family history of a mood disorder
- Residual symptoms *[Guideline]*

Other risk factors for recurrence include the presence of a general medical condition, ongoing psychosocial stressors, negative cognitive styles, and persistent sleep disturbance *[Guideline]*.

Maintenance therapy should also be considered for at-risk patients with double depression and patients with comorbid anxiety disorder or substance abuse. Patients whose major depression has a seasonal pattern are also at risk for recurrence and may benefit from seasonal reinstatement of light therapy or antidepressant therapy. For patients on maintenance medication, contacts can occur every 3 to 12 months if everything else is stable *[Low Quality Evidence]*, *[High Quality Evidence]*.

Pharmacotherapy

The dose of antidepressant medication that leads to satisfactory acute therapeutic response should be maintained during long-term treatment to reduce the risk for relapse and recurrence of depression *[Low Quality Evidence]*, *[High Quality Evidence]*.

When considering how long to continue medication after the remission of acute symptoms, two issues need to be considered: maintenance and prophylactic treatment. Patients who require several medication changes to achieve remission of an acute major depressive episode have a higher rate of relapse and a shorter period of time until relapse in comparison to patients who require fewer medication changes to achieve remission *[High Quality Evidence]*.

Significant data support the efficacy of antidepressants in preventing the recurrence of a major depressive episode. Although more research needs to be conducted, findings indicate that patients who are at highest risk of future episodes have had multiple prior episodes or were older at the time of the initial episode *[High Quality Evidence]*. These patients are candidates for long-term or lifetime prophylactic treatment.

For use of antidepressant medication, the following is recommended:

Table. Depression Medication Treatment Duration Based on Episode (see the original guideline document for International Classification of Disease [ICD]-9 codes associated with each episode)

Episode	Treatment Duration*
1st episode (major depression, single episode)	• Acute phase typically lasts 6-12 weeks. • Continue psychotherapy/medication treatment for 4-9 months once remission is reached. • Total = approximately 6-12 months
2nd episode (major depression, recurrent)	Continue medication treatment for 3 years once remission is reached. Withdraw gradually.
Persistent depressive disorder or 3+ episodes or 2 episodes (major depression, recurrent) with complicating factors such as: • Rapid recurrent episodes • More than 60 years of age at onset of major depression • Severe episodes or family history	Continue medication treatment indefinitely.

[Guideline], *[High Quality Evidence]*

*Treat to remission. Full remission is defined as a two-month absence of symptoms.

Analysis suggests that recurrence rates are reduced by 70% when patients are maintained on antidepressants for three years following their previous episode (average recurrence on placebo 41% versus 18% on active treatment) *[Low Quality Evidence]*.

Discontinuation of Pharmacotherapy

Premature treatment discontinuation can be triggered by a number of factors, including lack of adequate education about the disease, failure on the part of either physician or the patient to establish goals for follow-up, psychosocial factors, and adverse side effects. Appropriate ongoing collaborative care for depression can increase remission rates to as much as 76% by 24 months *[High Quality Evidence]*.

Complicating factors are those situations where evidence either shows or suggests higher rates of recurrence after stopping antidepressants. Such factors include:

- Pre-existing persistent depressive disorder
- Inability to achieve remission
- Recurrence of symptoms in response to previously attempted lowering dose or discontinuation of pharmacotherapy

[Low Quality Evidence]

If discontinuation of treatment is thought to be appropriate or necessary despite the known risks, a plan of action should be in place for prompt intervention if relapse occurs *[Low Quality Evidence]*.

In general, it is recommended that the dose be tapered over a period of weeks to several months when discontinuing an antidepressant. (Note that this approach is only feasible when the starting dose is lower than the therapeutic dose.)

The various existing antidepressants exhibit a wide array of half-lives and therapeutic dose ranges. Therefore, a discussion of detailed discontinuation strategies is beyond the scope of this guideline.

See also Annotation #11, "Evaluate Dose, Duration, Type and Adherence with Medication and/or Psychotherapy. Reconsider Accuracy of Diagnosis and Impact of Comorbidities."

11. Evaluate Dose, Duration, Type and Adherence with Medication and/or Psychotherapy. Reconsider Accuracy of Diagnosis or Impact of Comorbidities
If remission has not been achieved when reevaluated up to six weeks later, consider:

- Reevaluating the diagnosis.
- The possibility of a bipolar diathesis. Bipolar patients require a different treatment approach and may not consistently come forward with their hypomanic, mixed, or manic histories *[Low Quality Evidence]*.

- Looking for comorbidities, such as substance abuse issues, and involving addiction specialists as needed.
- Consulting with a behavioral health clinician if there are personality disorders present.
- Whether adequate engagement of patient/family exists and whether recommendations are being followed (adherence).
- Adding cognitive psychotherapy or adding another medication such as buspirone or bupropion. Both augmentation strategies showed similar improvement rates in the STAR*D study; however, the addition of medication resulted in a significantly more rapid response *[High Quality Evidence]*.
- Switching to a different antidepressant medication. After a failed trial of citalopram, remission rates in the STAR*D studies were 21.3% for bupropion sustained release (SR), 17.6% for sertraline, and 24.8% for venlafaxine XR *[High Quality Evidence]* although the differences were not statistically significant. Failure of a drug in one family does not rule out possible benefit from other drugs in that family. This is particularly true for SSRIs *[Low Quality Evidence]*.
- Augmentation strategies (such as lithium or low-dose thyroid). See Annotation #12, "Consider Other Strategies" below.
- Making a referral to psychiatry for possible MAOI or ECT. Many patients unresponsive to tricyclics are responsive to MAOIs. Rarely, the combination of tricyclics and MAOIs is used. This combination should be undertaken with extreme caution. Studies measuring response to MAOIs in SSRI non-responders have not been done *[Low Quality Evidence]*, *[High Quality Evidence]*. See Annotation #12, "Consider Other Strategies."
- Adding, switching or substituting treatment modality. A switch from an antidepressant to psychotherapy or vice versa appears useful for non-responders to initial treatment *[Low Quality Evidence]*. If there is less than 25% reduction of symptoms after six weeks at therapeutic dose (i.e., partial positive response to medication), add, switch or substitute another treatment modality. If there is a partial medication response and side effects are not prohibitive, increase the dose. As part of the evaluation, use a standardized assessment tool to gauge progress.

Pharmacologic Therapy

Without long-term antidepressant treatment, major depressive relapses and recurrences occur in 50% to 80% of patients. Double-blind discontinuation studies reveal that antidepressants decrease the risk of relapse and recurrence and have repeatedly shown antidepressants to be more efficacious than placebo substitution.

It has been well established that raising the dose of tricyclics or MAOIs may improve response. Similarly, a controlled study showed that raising the dose of fluoxetine (from 20 mg to 40 or 60 mg) in partially responsive patients was more effective than adding desipramine (25 to 50 mg per day) or lithium (300 to 600 mg daily). In non-responders, raising the fluoxetine dose was as effective as adding lithium, and both were more effective than adding desipramine *[High Quality Evidence]*, *[Low Quality Evidence]*.

One study with a tricyclic antidepressant showed decreased risk of relapse after 18 months of treatment *[Low Quality Evidence]*.

Surveys of patient populations have indicated that patients receiving prescriptions for one of the benzodiazepines or other minor tranquilizers or hypnotics tend to use less than prescribed and to reduce their use over time. Benzodiazepine abuse is usually seen as part of a pattern of abuse of multiple drugs often involving alcohol and sometimes opioids *[Low Quality Evidence]*.

See also "Discuss Treatment Options" section in Annotation #8 and Annotation #10, "Continuation and Maintenance Treatment Duration Based on Episode."

12. Consider Other Strategies
    - Augmentation strategies may be considered for partial responders, and combinations of antidepressants (when each has a different mechanism) have been shown to be options in those who fail to achieve remission.
    - If patients do not respond to intensive outpatient treatment, partial or full hospitalization may be considered in patients who have not responded to outpatient management, particularly if safety issues are a concern.
    - Use of bright light therapy for treatment of major depression with a seasonal specifier is well established.
    - Electroconvulsive treatment is effective and can sometimes be administered safely in an outpatient setting.

    Treatment-resistant depression has several definitions in the literature. It is important to distinguish treatment resistance from a lack of completion of a full course of treatment. The literature tends to focus on pharmacological treatments in the definition of treatment resistance without consistently incorporating psychotherapeutic modalities. True treatment resistance is seen as occurring on a continuum, from failure to reach remission after an adequate trial of a single antidepressant to failure to achieve remission despite several trials of antidepressants, augmentation strategies, ECT and psychotherapy. For the purposes of making recommendations for primary care clinicians, the guideline developers define true treatment resistance as failure to achieve remission with an adequate trial of therapy and three different classes of antidepressants at adequate duration and dosage *[High Quality Evidence]*, *[Low Quality Evidence]*, *[Systematic Review]*.

    Augmentation Therapy

Augmentation therapy is used for those situations in which the patient's depression is either treatment-resistant or partially responsive to treatment. This is a good time to consult and/or refer to a mental health specialist.

Augmentation methods include:

- Bupropion or buspirone-SSRI combination *[High Quality Evidence]*, *[Low Quality Evidence]*
- Mirtazapine-SSRI combination *[High Quality Evidence]*, *[Low Quality Evidence]*
- Triiodothyronine (T_3) augmentation of antidepressants *[High Quality Evidence]*, *[Low Quality Evidence]*
- Stimulant augmentation of TCA-SSRI ("jump-start response") *[Low Quality Evidence]*, *[High Quality Evidence]*, *[Systematic Review]*
- TCA-SSRI combination (caution — elevated TCA level – to be monitored) *[Low Quality Evidence]*
- Lithium augmentation with TCAs. Lithium augmentation with SSRI (caution — case reports of serotonin syndrome) *[High Quality Evidence]*, *[Low Quality Evidence]*
- Atypical antipsychotic-antidepressant combination *[Systematic Review]*, *[Meta-analysis]*, *[High Quality Evidence]*

Hospitalization

Partial or full hospitalization may be indicated in patients with unrelenting depressive symptoms, particularly if safety issues are a concern. The Reducing Avoidable Readmissions Effectively (RARE) Campaign (http://www.RAREreadmissions.org) has demonstrated effectiveness at avoiding readmissions to the emergency room or hospital. Five key areas of improvement identified by the program include Patient/Family Engagement and Activation, Medication Management, Comprehensive Transition Planning, Care Transition Support and Transition Communication.

The most important consideration from a primary care standpoint is having follow-up visits for chronic or acute physical problems arranged with their clinician prior to hospital discharge. Patients without a primary care clinician should be connected with one within 60 days of hospital discharge for a physical assessment and preventive interventions to help decrease the rate of readmission.

The following are most commonly referred from a primary care setting. For other specialized therapies, see Appendix H, "Specialized Therapies," in the original guideline document.

Electroconvulsive Therapy (ECT)

Response and remission rates are higher with ECT than with any other form of antidepressant treatment, with 70% to 90% of patients showing improvement *[High Quality Evidence]*, *[Systematic Review]*. Patients may express a choice for ECT; shared decision-making should be engaged to determine if it is appropriate. Electroconvulsive treatment is usually performed on an inpatient basis, but for some individuals, it can be administered safely in an outpatient setting. A patient considering ECT would need to be able to tolerate anesthesia, and should consult with a psychiatrist about the risks and benefits *[Systematic Review]*, *[High Quality Evidence]*.

In addition to its use as a treatment in the acute phase, ECT is an effective maintenance therapy for major depression. One study compared continuous ECT versus nortriptyline and lithium treatment and found no difference in relapse rates *[High Quality Evidence]*.

ECT is also effective for treating major mental illness during pregnancy, and the risks of adverse events are low. It should be strongly considered in pregnant women with severe symptoms of mental illness, such as psychotic symptoms, catatonia or strong suicidal urges *[Systematic Review]*.

Factors that may suggest a given patient may be an ECT candidate include:

- Geriatric depression *[Systematic Review]*
- If antidepressant medications have not been tolerated or pose a significant medical risk
- If antidepressant medication trials have not been successful
- If ECT has been successful in previous episodes
- If catatonia is present
- When a rapid response is needed because of severe suicide risk or because the patient's health has been significantly compromised by the depression (e.g., severe cachexia, inability to attend to the activities of everyday living). ECT has been shown to be effective in resolving expressed suicidal intent *[High Quality Evidence]*.
- If depression with psychotic features
- If melancholic symptoms are predominant
- Depression and Parkinsonism

[Guideline]

Common side effects associated with ECT include headaches, myalgias, nausea, drowsiness, confusion, and amnesia. More serious and rare side effects include hypertension, tachycardia, myocardial infarction, cerebrovascular accident, or death.

Light Therapy

Use of bright light therapy for treatment of major depression with a seasonal specifier is well established *[High Quality Evidence]*, *[Meta-analysis]*. Additionally, there is evidence to support the use of bright light therapy for other types of depressive symptom patterns, including non-seasonal depression and milder variations of seasonal depressive patterns *[Systematic Review]*, *[High Quality Evidence]*. For non-seasonal depression, light therapy's benefit as an adjunctive treatment is more robust than its benefit as monotherapy *[Systematic Review]*. Bright light therapy may also quicken and enhance the effects of antidepressant medication *[High Quality Evidence]*. In two small pilot studies, promising results were seen in pregnant and postpartum women with non-seasonal depression *[High Quality Evidence]*, *[Low Quality Evidence]*.

Dosage. The standard starting dose for depression with a seasonal specifier is 10,000 lux for 30 minutes each morning *[Systematic Review]*. Research on bright light therapy for other types of depression has not necessarily utilized standard dosages and exposure times.

Side effects. The most common side effects are nausea, jitteriness, and headache *[Systematic Review]*.

Equipment. It is important for light therapy treatment to utilize equipment that eliminates ultraviolet frequencies and produces bright light of known spectrum and intensity. For these reasons, use of client-constructed light therapy units is contraindicated.

Overall recommendation. The American Psychiatric Association (APA) Task Force concluded that "light therapy is an evidence-based, effective, well-tolerated treatment for seasonal affective disorder, as well as an augmentation strategy for antidepressant treatment of nonseasonal depression" *[Systematic Review]*.

See Appendix H, "Specialized Therapies," in the original guideline document for other more specialized therapies available.

Definitions:

Quality of Evidence and Strength of Recommendations

Category	Quality Definitions	Strong Recommendation	Weak Recommendation
High Quality Evidence	Further research is very unlikely to change confidence in the estimate of effect.	The work group is confident that the desirable effects of adhering to this recommendation outweigh the undesirable effects. This is a strong recommendation for or against. This applies to most patients.	The work group recognizes that the evidence, though of high quality, shows a balance between estimates of harms and benefits. The best action will depend on local circumstances, patient values or preferences.
Moderate Quality Evidence	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.	The work group is confident that the benefits outweigh the risks, but recognizes that the evidence has limitations. Further evidence may impact this recommendation. This is a recommendation that likely applies to most patients.	The work group recognizes that there is a balance between harms and benefit, based on moderate quality evidence, or that there is uncertainty about the estimates of the harms and benefits of the proposed intervention that may be affected by new evidence. Alternative approaches will likely be better for some patients under some circumstances.
Low Quality Evidence	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change. The estimate or any estimate of effect is very uncertain.	The work group feels that the evidence consistently indicates the benefit of this action outweighs the harms. This recommendation might change when higher quality evidence becomes available.	The work group recognizes that there is significant uncertainty about the best estimates of benefits and harms.

Clinical Algorithm(s)

A detailed and annotated clinical algorithm titled "Adult Depression in Primary Care" is provided in the original guideline document .

An example suicidality screening flow is available in Appendix C of the original guideline document .

Scope

Disease/Condition(s)

- Major depression
- Persistent depressive disorder

Note: Diagnoses outside the scope of this guideline include adjustment disorder and bipolar disorder.

Other Disease/Condition(s) Addressed

- Cardiovascular disease
- Chronic pain
- Diabetes
- Insomnia
- Panic disorder
- Substance-related disorders

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Screening

Treatment

Clinical Specialty

Family Practice

Geriatrics

Internal Medicine

Obstetrics and Gynecology

Psychiatry

Psychology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Health Plans

Hospitals

Managed Care Organizations

Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Guideline Objective(s)

- To assist primary care in developing systems that support effective assessment, diagnosis and ongoing management of initial and recurrent major depression and persistent depressive disorder in adults age 18 and over and assist patients to achieve remission of symptoms, reduce relapse and return to previous level of functioning
- To increase the percentage of patients accurately diagnosed with major depression or persistent depressive disorder
- To decrease the number of completed suicides in patients with major depression or persistent depressive disorder managed in primary care
- To increase the percentage of patients with major depression or persistent depressive disorder who are assessed for the presence and severity (mild to moderate, moderate to high) and dependent on substance misuse
- To increase the assessment for major depression or persistent depressive disorder of primary care patients presenting with additional high-risk conditions such as diabetes, cardiovascular disease, post-stroke, chronic pain and all perinatal women
- To improve communication between the primary care physician and the mental health care clinician (if patient is co-managed)
- To increase the percentage of patients with major depression or persistent depressive disorder who have improvement in outcomes from treatment for major depression or persistent depressive disorder
- To increase the percentage of patients with major depression or persistent depressive disorder who have a follow-up to assess of response to treatment

Target Population

Adults age 18 and over with suspected or established diagnosis of major depression and persistent depressive disorder

Note: This guideline does not address the pediatric population.

Interventions and Practices Considered

Diagnosis/Evaluation/Screening

1. Standardized screening instrument for depression if suspected
2. Diagnosis and characterization of major depression with clinical interview, including use of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or clinical criteria
3. Patient history
4. Assessment of suicide risk
5. Assessment for substance misuse or psychiatric comorbidity
6. Consideration of medical comorbidities, cultural considerations, and special populations (geriatrics, pregnancy)

Treatment/Management

1. Comprehensive treatment plan with shared decision-making
    - Use of collaborative care approach

- Patient education and engagement
- Written and mutually agreed-upon plan
- Discussion of treatment options (psychotherapy, pharmacotherapy)
- Establish and maintain follow-up

2. Evaluation of patient's response and maintenance therapy
3. Other strategies
    - Augmentation therapy (i.e., combinations of different classes of antidepressants)
    - Hospitalization
    - Electroconvulsive treatment (ECT)
    - Light therapy

Major Outcomes Considered

- Prevalence of depression in the general population
- Sensitivity and specificity of screening tools
- Risk for and rate of suicide or suicide attempts
- Rates of remission, recurrence, relapse, and recovery
- Adverse effects of treatment options

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A consistent and defined process is used for literature search and review for the development and revision of Institute for Clinical Systems Improvement (ICSI) guidelines. The literature search was divided into two stages to identify systematic reviews (stage I) and randomized controlled trials, meta-analyses and other literature (stage II). Literature search terms used for this revision include acupuncture and yoga, persistent depressive disorder, anxiety, panic disorder, psychotherapy, pain, diabetes and heart failure in depressed patients. The search was performed in PubMed from January 2012 through December 2012.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence and Strength of Recommendations

Category	Quality Definitions	Strong Recommendation	Weak Recommendation
High Quality Evidence	Further research is very unlikely to change confidence in the estimate	The work group is confident that the desirable effects of adhering to this recommendation outweigh the	The work group recognizes that the evidence, though of high quality, shows a balance between estimates of harms and benefits. The best action will depend on local

Category	Quality Definitions	Strong Recommendation	Weak Recommendation
	of effect.	undesirable effects. This is a strong recommendation for or against. This applies to most patients.	circumstances, patient values or preferences.
Moderate Quality Evidence	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.	The work group is confident that the benefits outweigh the risks, but recognizes that the evidence has limitations. Further evidence may impact this recommendation. This is a recommendation that likely applies to most patients.	The work group recognizes that there is a balance between harms and benefit, based on moderate quality evidence, or that there is uncertainty about the estimates of the harms and benefits of the proposed intervention that may be affected by new evidence. Alternative approaches will likely be better for some patients under some circumstances.
Low Quality Evidence	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change. The estimate or any estimate of effect is very uncertain.	The work group feels that the evidence consistently indicates the benefit of this action outweighs the harms. This recommendation might change when higher quality evidence becomes available.	The work group recognizes that there is significant uncertainty about the best estimates of benefits and harms.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

New Guideline Development Process

A work group consisting of 6 to 12 members that includes physicians, nurses, pharmacists, other healthcare professionals relevant to the topic, and an Institute for Clinical Systems Improvement (ICSI) staff facilitator develops each document. Ordinarily, one of the physicians will be the leader. Most work group members are recruited from ICSI member organizations, but if there is expertise not represented by ICSI members, 1 or 2 work group members may be recruited from medical groups, hospitals or other organizations that are not members of ICSI. Patients on occasion are invited to serve on work groups.

The work group will meet for 7 to 8 three-hour meetings to develop the guideline. A literature search and review is performed and the work group members, under the coordination of the ICSI staff facilitator, develop the algorithm and write the annotations and literature citations.

Once the final draft copy of the guideline is developed, the guideline goes to the ICSI members for critical review.

Revision Process of Existing Guidelines

ICSI scientific documents are revised every 12 to 24 months as indicated by changes in clinical practice and literature. For documents that are revised on a 24-month schedule, ICSI checks with the work group on an annual basis to determine if there have been changes in the literature significant enough to cause the document to be revised earlier or later than scheduled. For yearly reviewed documents, ICSI checks with every work group 6 months before the scheduled revision to determine if there have been changes in the literature significant enough to cause the

document to be revised earlier than scheduled.

Literature Search

ICSI staff, working with the work group to identify any new pertinent clinical trials, systematic reviews, or regulatory statements and other professional guidelines, conduct a literature search.

Revision

A second review by members is indicated if there are changes or additions to the document that would be unfamiliar or unacceptable to member organizations. If a review by members is not needed, the document goes to the appropriate steering committee for approval according to the criteria outlined in the "Description of Method of Guideline Validation" field.

Rating Scheme for the Strength of the Recommendations

See the "Rating Scheme for the Strength of the Evidence" field.

Cost Analysis

Cost-Effectiveness Impact of Collaborative Care Models

Most studies have concluded that creating and implementing a collaborative care model will increase effectiveness – producing significant and sustained gains in "depression-free days." The six-month and one-year studies show increased cost to the outpatient care system. This is balanced by continuous accumulation of clinical and economic benefits over time. One of the factors is the decrease in the utilization of general medical services in patients with chronic medical comorbidities. The two-year studies show mixed results possibly indicating a turning point, and the only longer-term study conducted was the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) study. This was a well-done study analyzing the costs of performing collaborative care for one year over a four-year period and illustrated a cost savings of $3,363 per patient over the four-year period.

Workplace Impact of Collaborative Care Models

Some randomized controlled trials looked at cost of doing enhanced care and specifically tallied decreases of "absenteeism" and improved work performance (which means that employees are present and effectively achieving good work results, sometimes referred to as decreasing "presenteeism"). Some studies monetized the results and compared them to usual care. The significance of these studies and this analysis is that in the United States, depression costs employers $24 billion in lost productive work time.

In two randomized controlled trials, employers received significant return on investment (ROI) from collaborative care treatment of depression by increasing productivity/decreasing absenteeism in the workplace. Increased productivity ranged from 2.6 hours to 5.6 hours per week after one year. Studies going out to two years showed continued gains in year two.

Several of the articles recommend consideration of coverage of collaborative care to ensure better patient outcomes and the ROI illustrated.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Critical Review Process

The purpose of critical review is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the guideline. Critical review also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes necessary across systems in their organization to implement the guideline.

All member organizations are expected to respond to critical review guidelines. Critical review of guidelines is a criterion for continued membership

within Institute for Clinical Systems Improvement (ICSI).

After the critical review period, the guideline work group reconvenes to review the comments and make changes, as appropriate. The work group prepares a written response to all comments.

Document Approval

Each document is approved by the Committee for Evidence-Based Practice (CEBP).

The committee will review and approve each guideline/protocol, based on the following criteria:

- The aim(s) of the document is clearly and specifically described.
- The need for and importance of the document is clearly stated.
- The work group included individuals from all relevant professional groups and had the needed expertise.
- Patient views and preferences were sought and included.
- The work group has responded to all feedback and criticisms reasonably.
- Potential conflicts of interest were disclosed and do not detract from the quality of the document.
- Systematic methods were used to search for the evidence to assure completeness and currency.
- Health benefits, side effects, risks and patient preferences have been considered in formulating recommendations.
- The link between the recommendation and supporting evidence is clear.
- Where the evidence has not been well established, recommendations based on community practice or expert opinion are clearly identified.
- Recommendations are specific and unambiguous.
- Different options for clinical management are clearly presented.
- Clinical highlights and recommendations are easily identifiable.
- Implementation recommendations identify key strategies for *health care systems* to support implementation of the document.
- The document is supported with practical and useful tools to ease *clinician* implementation.
- Where local resource availability may vary, alternative recommendations are clear.
- Suggested measures are clear and useful for quality/process improvement efforts.

Once the document has been approved, it is posted on the ICSI Web site and released to members for use.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is classified for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis and management of primary care patients with major depression or persistent depressive disorder

Potential Harms

Side Effects of Anti-Depressant Medication

- *Selective serotonin re-uptake inhibitors (SSRIs), as well as venlafaxine, duloxetine, mirtazapine and bupropion*, may cause headache, nervousness, insomnia, and sexual side effects. They also may be more expensive because some may not yet be available as generics.
- Although *tricyclic antidepressants (TCAs)* are effective against depression, they are associated with cardiovascular side effects including orthostatic hypotension, slowed cardiac conduction, proarrhythmic activity, and increased heart rate.
- In 2011, the Food and Drug Administration (FDA) published a "Medwatch" drug safety alert regarding the potential risk of abnormal heart

rhythms associated with *citalopram* doses greater than 40 mg a day due to concerns about prolonged QT interval prolongation and the risk for torsades de pointes. Prescribers were initially told to avoid using citalopram doses higher than 40 mg and discouraged from using it at all in patients with congenital long QT syndrome, bradyarrhythmias, congestive heart failure, or at risk for developing hypokalemia or hypomagnesemia. In March 2012 this was revised by downgrading the warning from "contraindicated" to "not recommended" for patients with congenital long QT syndrome because patients with this condition have few viable alternative treatments. Ongoing monitoring was suggested, a maximum dose of 20 mg/day was recommended for age >60, and discontinuation was recommended when QTc >500ms. A recent review of Veterans Health Administration patients who were prescribed citalopram between 2004 and 2009 (N=618,450) found daily doses of citalopram greater than 40 mg a day were associated with lower risks of ventricular arrhythmias, all-cause mortality, and non-cardiac mortality, compared with lower doses of citalopram. Overall, no increased risks of cardiac mortality were observed. These results were similar when compared with a cohort of patients prescribed sertraline (N=365,898) during the same time period.

- *Secondary amine tricyclics* are used less frequently as first-line therapy because of associated side effects. These medications should be monitored cautiously in patients with heart problems, or in patients with potential for drug interactions. Monitoring blood levels and electrocardiogram may be advised.
- *Monoamine oxidase inhibitors (MAOIs)* should be restricted for patients who do not respond to other treatments because of their potential for serious side effects and the necessity of dietary restrictions.
- Many *antidepressant agents* have clinically significant drug interactions, particularly those agents that undergo cytochrome P450 enzymatic metabolism in the liver.
- *TCA-SSRI combination* should be given with caution as it increases TCA levels. Common adverse reactions of tricyclic antidepressants include anticholinergic and sedative effects. Antidepressant medications with anticholinergic side effects contribute to dry mouth/xerostomia, caries, gingivitis and periodontal disease.
- *Stimulant drugs' augmentation of TCA-SSRI*: cases of sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant medication at usual doses for attention-deficit hyperactivity disorder (ADHD). Adults with serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease or other serious cardiac problems should not be treated with stimulant medications.
- Rarely, the combination of *tricyclics* and *MAOIs* is used. This combination should be undertaken with extreme caution.

Drug Interactions

- *Lithium augmentation with SSRIs* poses the risk of serotonin syndrome. Serotonin syndrome is a potentially life-threatening, pharmacodynamic drug interaction resulting in excessive nervous system levels of serotonin. Patients experiencing this reaction may present with mental status changes such as anxiety, confusion, delirium or coma. Autonomic symptoms may include tachycardia, labile blood pressure and hyperthermia. Muscle rigidity, ataxia, tremor, myoclonus and other neurologic symptoms are also common. The higher levels of intrasynaptic serotonin caused by combinations of MAOIs with an SSRI are likely to cause hyperpyrexia and death.
- *Atypical antipsychotic-antidepressant combination*: Patients receiving aripiprazole experienced higher rates of akathisia and fatigue, compared to those randomized to placebo
- Many drugs interact with *St. John's wort*, including other antidepressants, warfarin, oral contraceptives, antiretroviral, anti-cancer and anti-rejection drugs. Care should be taken to ask all patients what medications they are taking, including over-the-counter and supplements, to avoid these interactions.

Other Therapies

- Common side effects associated with *electroconvulsive therapy (ECT)* include headaches, myalgias, nausea, drowsiness, confusion and amnesia. More serious and rare side effects include hypertension, tachycardia, myocardial infarction, cerebrovascular accident, or death.
- The most common side effects of *light therapy* are nausea, jitteriness, and headache.

Subgroups Most Likely to Be Harmed

- *Elderly patients*: Because of the potential for decreased renal and hepatic function, concomitant diseases and medications, the elderly are at higher risk of significant side effects or drug interactions with antidepressant medications. Tertiary amine tricyclics should generally be avoided in elderly patients because of the high incidence of orthostatic hypotension, sedation, cognitive problems, and cardiac effects with these agents.
- *Pregnant women*: Medications taken during pregnancy are considered teratogenic if they increase the risk of congenital malformations above the baseline risk of 3% to 4%.
- *Neonatal toxicity*: Prenatal exposure to antidepressants has been associated with transient symptoms of possible medication withdrawal or toxicity in neonates. These neonatal syndromes have been described with most TCAs, SSRIs and non-SSRIs and can include jitteriness, irritability, breathing difficulties, bowel obstruction and urinary retention.

- *Nursing women*: Clinicians should advise nursing women on psychotropic medications to monitor infants for behavioral changes, such as excessive sedation, jitteriness or inconsolable crying. Infants who develop these symptoms should be evaluated by their clinician for possible drug toxicity. For infants who are premature or have any medical problems, mothers on psychotropic medication who choose to breastfeed could consider pumping and storing/discarding breast milk until the infant is healthy and can metabolize medication more efficiently.

Contraindications

Contraindications

Use of client-constructed light therapy units is contraindicated.

Qualifying Statements

Qualifying Statements

- The information contained in this Institute for Clinical Systems Improvement (ICSI) Health Care Guideline is intended primarily for health professionals and other expert audiences.
- This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients and families are urged to consult a health care professional regarding their own situation and any specific medical questions they may have. In addition, they should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in their individual case.
- This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition.

Implementation of the Guideline

Description of Implementation Strategy

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment and tobacco cessation.

Implementation Recommendations

Prior to implementation, it is important to consider current organizational infrastructure that address the following:

- System and process design
- Training and education
- Culture and the need to shift values, beliefs and behaviors of the organization

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

- Detection and diagnosis
  - Systems in place to reliably determine if a patient is depressed
  - Use of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and structured questionnaires (such as

Patient Health Questionnaire-9 [PHQ-9])

- Patient-centered care, education and self-management programs
  - Structured attention to patient preferences
  - Patient and family education materials/protocols
  - Patient self-management skills such as journal writing or self-monitoring
    When appropriate, encourage family or loved ones to attend appointments for patient support and advocacy
  - Involving families as well in care management programs.
  - Care manager role to coordinate the disease management for patients with depression including such things as patient contacts, education, self-management tools and tips
- Mental health/behavioral medicine specialist involvement
  - Shared care — collaborative care between behavioral health specialists and primary care clinicians in the primary care setting. Care manager and/or primary care clinician consulting with psychiatry on a regular basis regarding the case load of patients with depression managed in the depression care management program
  - Appointment availability — access to behavioral health in timely manner
- Outcomes measurement
  - Build in plans for outcome measures as well as ongoing process measures
  - Response rate to various treatments
  - Remission rates — improvement in response is stable over time
- Systems to coordinate care, ensure continuity and keep clinicians informed of status
  - Build automated processes for the first four core elements wherever possible
  - Reduce dependence on human behavior to ensure delivery of patient care processes
  - Use of components of the chronic care model for depression care (e.g., use of registries, community outreach)
  - Structured frequent monitoring and follow-up with patient
  - Nurse/care manager phone care and use of other modalities for patient follow-up

Implementation Tools

Chart Documentation/Checklists/Forms

Clinical Algorithm

Quality Measures

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Mitchell J, Trangle M, Degnan B, Gabert T, Haight B, Kessler D, Mack N, Mallen E, Novak H, Rossmiller D, Setterlund L, Somers K, Valentino N, Vincent S. Adult depression in primary care. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Sep. 129 p. [334 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1996 Jan (revised 2013 Sep)

Guideline Developer(s)

Institute for Clinical Systems Improvement - Nonprofit Organization

Guideline Developer Comment

The Institute for Clinical Systems Improvement (ICSI) is comprised of 50+ medical group and hospital members representing 9,000 physicians in Minnesota and surrounding areas, and is sponsored by five nonprofit health plans. For a list of sponsors and participating organizations, see the ICSI Web site.

Source(s) of Funding

- The Institute for Clinical Systems Improvement (ICSI) provided the funding for this guideline. The annual dues of the member medical groups and sponsoring health plans fund ICSI's work. Individuals on the work group are not paid by ICSI, but are supported by their medical group for this work.
- ICSI facilitates and coordinates the guideline development and revision process. ICSI, member medical groups, and sponsoring health plans review and provide feedback, but do not have editorial control over the work group. All recommendations are based on the work group's independent evaluation of the evidence.

Guideline Committee

Committee on Evidence-Based Medicine

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Financial Disclosures/Conflicts of Interest

The Institute for Clinical Systems Improvement (ICSI) has long had a policy of transparency in declaring potential conflicting and competing interests of all individuals who participate in the development, revision and approval of ICSI guidelines and protocols.

In 2010, the ICSI Conflict of Interest Review Committee was established by the Board of Directors to review all disclosures and make recommendations to the board when steps should be taken to mitigate potential conflicts of interest, including recommendations regarding removal of work group members. This committee has adopted the Institute of Medicine Conflict of Interest standards as outlined in the report Clinical Practice Guidelines We Can Trust (2011).

Where there are work group members with identified potential conflicts, these are disclosed and discussed at the initial work group meeting. These members are expected to recuse themselves from related discussions or authorship of related recommendations, as directed by the Conflict of Interest committee or requested by the work group.

The complete ICSI policy regarding Conflicts of Interest is available at the ICSI Web site .

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Financial/Non-Financial Conflicts of Interest: None

Guideline Status

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

Guideline Availability

Electronic copies of the updated guideline: Available from the Institute for Clinical Systems Improvement (ICSI) Web site .

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org ; e-mail: icsi.info@icsi.org.

Availability of Companion Documents

The following is available:

- Major depression in adults in primary care. Executive summary. Bloomington (MN): Institute for Clinical Systems Improvement; 2013 May. 3 p. Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site .

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org ; e-mail: icsi.info@icsi.org.

In addition, several checklists and questionnaires, including the Patient Health Questionnaire (PHQ-9), the Hamilton Rating Scale for Depression (HAM-D), the Cornell Scale for Depression in Dementia, the Geriatric Depression Scale, and others, are available in the appendices to the original guideline document .

Patient Resources

None available

NGC Status

This summary was completed by ECRI on April 30, 1999. The information was verified by the guideline developer as of April 30, 1999. This summary was updated on December 4, 2002. The updated information was verified by the guideline developer on December 24, 2002. This summary was updated again on August 17, 2004. This summary was updated by ECRI on August 15, 2005, following the U.S. Food and Drug Administration advisory on antidepressant medications. This summary was updated by ECRI on October 3, 2005, following the U.S. Food and Drug Administration advisory on Paxil (paroxetine). This summary was updated by ECRI on December 12, 2005, following the U.S. Food and Drug Administration advisory on Paroxetine HCL - Paxil and generic paroxetine. This summary was updated by ECRI on June 13, 2006. This summary was updated by ECRI on November 22, 2006, following the FDA advisory on Effexor (venlafaxine HCl). This NGC summary was updated by ECRI Institute on July 6, 2007. The updated information was verified by the guideline developer on September 13, 2007. This summary was updated by ECRI Institute on November 9, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This summary was updated by ECRI Institute on January 10, 2008, following the U.S. Food and Drug Administration advisory on Carbamazepine. This summary was updated by ECRI Institute on July 18, 2008. This summary was updated by ECRI Institute on May 1, 2009 following the U.S. Food and Drug Administration advisory on antiepileptic drugs. This NGC summary was updated by ECRI Institute on December 22, 2009 and November 10, 2010. This summary was updated by ECRI Institute on May 20, 2011 following the U.S. Food and Drug Administration advisory on antipsychotic drugs. This NGC summary was updated by ECRI Institute on September 21, 2011. This summary was updated by ECRI Institute on April 16, 2012 following the updated U.S. Food and Drug Administration advisory on Celexa (citalopram hydrobromide). This NGC summary was updated by ECRI Institute on August 3, 2012. This summary was updated by ECRI Institute on January 23, 2013 following the U.S. Food and Drug Administration advisory on Zolpidem containing products. This NGC summary was updated by ECRI Institute on January 23, 2014. This summary was updated by ECRI Institute on May 22, 2014 following the U.S. Food and Drug Administration advisory on Eszopiclone (Lunesta). This summary was updated by ECRI Institute on May 24, 2016 following the U.S. Food and Drug Administration advisory on Olanzapine. This summary was updated by ECRI Institute on May 31, 2016 following the U.S. Food and Drug Administration advisory on Aripiprazole (Abilify, Abilify Maintena, Aristada).

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